REMARKS

Claims 1-62 were pending in the present application. Claims 3-5, 10, 15-20, 24, 25, 29, 36, 38-41, 43, 50 and 57 were withdrawn from consideration. By virtue of this response, claims 1, 8, 10-12, 30, and 37 have been amended, claims 2-7, 9, 15-20, 23-25, and 42-60 have been cancelled, and new claim 63 has been added. Accordingly, claims 1, 8, 11-14, 21-22, 26-28, 30-35, 37, and 61-63 are currently under consideration.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and, moreover, has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation, continuation-in-part, and/or divisional applications.

Amendments to the Specification

The descriptions of Figures 2 and 3 in the "Brief Descriptions of the Figures" section of the specification have been amended to correct an inadvertent error in the description of these figures. Support for these amendments can be found, e.g., at lines 14-16 of page 60 (description of results shown in Figure 2) and at lines 17-19 of page 61 (description of results shown in Figure 3). No new matter is added.

Claim Amendments

As noted above, claims 1, 8, 10-12, 30, and 37 have been amended. Claims 2-7, 9, 15-20, 23-25, and 42-60 have been cancelled. New claim 63 has been added.

Claim 1 has been amended to indicate that the marker of de novo fatty acid synthesis comprises: (a) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the free fatty acid fraction of the blood product, wherein the method is a method to assess de novo fatty acid synthesis in adipose tissue; or (b) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the phosphatidylcholine or cholesterol ester fraction of the blood product, wherein

the method is a method to assess de novo fatty acid synthesis in liver tissue. Support for this amendment is found, e.g., at lines 3-10 of page 16, lines 13-22 of page 23, lines 6-22 of page 34, lines 2-8 of page 35, lines 11-28 of page 60, and original claims 2, 6-8, 9, 10-11, and 12.

Claims 8 and 12 are amended for consistency with amended claim 1.

Claims 10 and 11 are amended due to the amendment of claim 1 and cancellation of claim 9.

Claims 11, 30, and 37 are all amended to delete reference to the lipid category "triglyceride." An apparent typographical error has also been corrected in amended claim 37.

New claim 63 finds support in original claim 11.

No new matter is added by the claim amendments.

Information Disclosure Statement

The Examiner has indicated that the listing of the references on the Information Disclosure Statement (Form PTO 1449) filed on April 15, 2004, is incomplete since the Siguel citation is missing the date of publication of the article. We are submitting herewith a Supplemental Information Disclosure Statement which includes the proper citation for the Siguel reference. References cited in the Declaration of Steven M. Watkins, submitted herewith, and/or in Applicants' remarks below that have not been previously submitted, as well as an additional reference, are also included with the Supplemental Information Disclosure Statement submitted herewith. Applicants respectfully request that the Examiner consider the Siguel reference and the other references provided with the Supplemental Information Disclosure Statement submitted herewith.

Claim Rejections under 35 U.S.C. § 112

Claims 1, 2, 6-9, 11-14, 21-23, 26-28, 30-35, 37, 42, 44-49, 51-56, and 58-62 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled for the full scope of the claims. The grounds for the rejection recited by the Examiner appear to be, in essence, that the specification (in light of the state of the art) allegedly does not teach a correlation between the level of palmitic acid or palmitoleic acid in plasma to (a) *de novo* fatty acid synthesis in the liver and/or (b) any condition or disease.

Applicants respectfully disagree and traverse this rejection.

By virtue of this Amendment, claim 1 has been amended, without prejudice. This amendment has been made to expedite prosecution of the immediate application and without acquiescing as to the merits of the rejection. Claim 1, as amended, is now directed to a method of assessing *de novo* fatty acid synthesis in a tissue of an organism, comprising quantifying a marker of *de novo* fatty acid synthesis in a biological sample from the organism, wherein the biological sample is a blood product, and wherein the marker of *de novo* fatty acid synthesis comprises: (a) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the free fatty acid fraction of the blood product, wherein the method is a method to assess *de novo* fatty acid synthesis in adipose tissue; or (b) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the phosphatidylcholine or cholesterol ester fraction of the blood product, wherein the method is a method to assess *de novo* fatty acid synthesis in liver tissue. The remainder of the rejected claims, claims 1, 8, 11-14, 21-22, 26-28, 30-34, and 61-62, are all dependent (directly or indirectly) on claim 1 and therefore incorporate all elements of claim 1. Claim 35 is also dependent upon claim 1 and is directed to a method of claim 1 wherein the quantity of the marker of *de novo* fatty acid synthesis is correlated to a propensity, risk, or metabolic basis for obesity of the organism. Claim 37 is dependent upon claim 35.

Claims 2-7, 9, 15-20, 23-25, 42, 44-49, 51-56, and 58-60 are cancelled by virtue of this Amendment without prejudice and, therefore, the rejection of these claims under 35 U.S.C. § 112,

first paragraph, is moot. These claims are cancelled in the interest of expediting allowance of the pending claims and without acquiescence as to the merits of the Examiners arguments.

Applicants contend that the claims as amended are fully enabled. The specification, as well as data from additional studies that are summarized in the Declaration of Steven M. Watkins, filed herewith, supports the full scope of the claims. The disclosures in the specification illustrate that, contrary to the Examiner's assertions, there is, in fact, a correlation between (a) palmitoleic acid (16:1n7) and/or the ratio of palmitoleic acid (16:1n7) to palmitic acid (16:0) in certain lipid classes, such as phosphatidylcholines, cholesterol esters, and free fatty acids, in blood and (b) *de novo* fatty acid synthesis in adipose or the liver and weight gain/loss. These experiments indicate that palmitoleic acid (16:1n7) and/or the ratio of palmitoleic acid (16:1n7) to palmitic acid (16:0) in certain lipid classes (e.g., phosphatidylcholines, cholesterol esters, and free fatty acids) can be used as markers for the assessment of *de novo* fatty acid synthesis and a propensity for weight gain/loss. Thus, the claims, as amended, are fully enabled by the disclosures of the specification and the additional data provided.

Applicants respectfully submit that, contrary to the Examiner's assertions, Example 1 at pages 38-62 of the specification does provide data that show a correlation exists between (a) the level of palmitoleic acid (16:1n7), as well as the ratio of palmitoleic acid (16:1n7) to palmitic acid (16:0), in certain lipid classes with (b) *de novo* fatty acid synthesis in adipose or the liver, as well as with weight gain/loss.

Example 1 reports the findings of a study in which the lipid composition in various tissues and plasma was measured in prediabetic mice (a cross of NZO and NON mouse strains) that had been treated with rosiglitazone, in NON mice that had been treated with CL316,243, and in control mice. Rosiglitazone is known to increase *de novo* fatty acid synthesis in adipose and the liver. See, e.g., McTernan, et al., *Diabetes* 51(5):1493-8, 2002, Patel et al., *Diabetes* 52(1):43-50, 2003, and Edvardsson et al., *Proteomics* 3(5):468-478, 2003 (included in the Supplemental Information Disclosure Statement submitted herewith). CL316,243, on the other hand, has been

shown to be linked to decreased lipogenesis. See, e.g., Ferrand et al., *J. Physiol. Biochem.* 62(2):89-99, 2006 (also included in the Supplemental Information Disclosure Statement submitted herewith).

The results of the study in Example 1 are shown in Tables 5-8 and described on pages 60-62 of the specification. Contrary to the Examiner's assertions at the bottom of page 3 of the Office Action mailed December 27, 2006, the specification does, in fact, identify the units of the quantities provided in Tables 5-8. Lines 6-8 of page 60 of the specification state, "In Tables 5 and 7, the data are expressed as nanomoles per gram of tissue or plasma. In tables 6 and 8, the data are expressed as a percentage of total fatty acids within each lipid class."

The lipid composition data in Tables 5-6 at pages 46-47 and 49-50 of the specification show that when rosiglitazone (i.e., a treatment known to increase *de novo* fatty acid synthesis) was given to the mice, the amount of palmitoleic acid in cholesterol esters in plasma, the amount of palmitoleic acid in phosphatidylcholines in plasma, and the amount of palmitoleic acid in free fatty acids in plasma all increased relative to control. The data in Tables 5-6 at pages 46-47 and 49-50 of the specification also show that when rosiglitazone was given to the mice, the ratio of palmitoleic acid to palmitic acid in cholesterol esters in plasma, the ratio of palmitoleic acid to palmitic acid in phosphatidylcholines in plasma, and the ratio of palmitoleic acid to palmitic acid in free fatty acids in plasma all increased relative to control.

As further indicated in Example 1 at page 61, lines 14-16, and Tables 7 and 8 of the specification, treatment of mice with CL316,243, on the other hand, induced a substantial decrease in palmitoleic acid concentrations in most lipid classes in heart, liver, adipose, and plasma. The lipid composition data in Tables 7 and 8 at pages 52, 58-59 of the specification show that when CL316,243 was administered to the mice, decreases in the level of palmitoleic acid, as well as in the ratio of palmitoleic acid to palmitic acid, in phosphatidylcholines in plasma, free fatty acids in plasma, and cholesterol esters in plasma relative to the controls were observed.

With respect to the results shown for mice treated with CL316,243, the Examiner states on page 4 of the Office Action mailed December 27, 2006, "The *de novo* fatty acid synthesis in the

liver, at least from an analysis of total fatty acid content, appears to be unaffected. Since experimental mice have tightly controlled diets and should have been paired fed for the experiments since the effect of diet on lipid content of the animal is well known, variation of total fatty acid content from the control to experimental should be some sort of measure of *de novo* synthesis." However, the Examiner has provided no citation that would suggest that total fat content in the liver would be an accurate reflection of hepatic fat synthesis and has no means of assessing how major factors that could affect total fat content in the liver (e.g., dietary intake, metabolic rate, cholesterol synthesis and bile acid secretions rates) were affected by the treatment of the mice with the drug. Thus, the Examiner has not provided adequate support for her assertion that *de novo* fatty acid synthesis is unaffected by CL316,243. As noted above, CL316,243 has been shown to be linked to decreased lipogenesis. See, e.g., Ferrand et al., *J. Physiol. Biochem.* 62(2):89-99, 2006.

In addition to measuring the lipid compositions, the body weight gain and adipose tissue weight gain of the mice in the study in Example 1 were also measured. The mice in the study that were given rosiglitazone showed a "significant increase" in both total body and adipose tissue weight, as stated in lines 14-16 of page 60 of the specification, whereas mice in the study that were given CL316,243 showed a "significant decrease" in both total body and adipose tissue weight as clearly stated in lines 17-19 of page 61 of the specification and shown in Figures 2 and 3. (Although the descriptions of Figures 2-3 on pages 5-6 of the specification contain obvious errors, these errors have been corrected by virtue of this Amendment.) Furthermore, as indicated at lines 11-13 of page 61 of the specification, clinical studies in humans have shown that patients taking rosiglitazone gain weight (Füchtenbusch et al., *Exp. Clin. Endocrinol. Diabetes* 108:151-163, 2000).

Thus, Applicants have demonstrated in Example 1 of the specification demonstrate that both palmitoleic acid and the ratio of palmitoleic acid to palmitic acid in certain lipid classes (e.g., cholesterol esters, phosphatidylcholines, and free fatty acids) in plasma positively correlate with rosiglitazone treatment, which in turn, positively correlates with *de novo* fatty acid synthesis in both adipose and the liver and correlates with weight gain. The experiments described in Example 1 also demonstrate that a decrease in the level of palmitoleic acid or in the ratio of palmitoleic acid to palmitic acid in certain lipid classes (e.g., cholesterol esters, phosphatidylcholines, and free fatty

acids) in plasma correlates with CL316,243 treatment, which in turn, correlates with decreased *de novo* fatty acid synthesis and with weight gain. These data support Applicants' claim that both palmitoleic acid and the ratio of palmitoleic acid to palmitic acid in certain lipid classes in plasma can be used as markers for *de novo* fatty acid synthesis in adipose and the liver and for a propensity for weight gain/loss.

In addition to the data originally presented in the specification, some data from additional studies have been obtained that further confirm that palmitoleic acid and the ratio of palmitoleic acid to palmitic acid in cholesterol esters plasma or serum can serve as markers of *de novo* fatty synthesis and weight gain/loss. These results further provide support for the enablement of the pending claims. The results of these additional experiments, Studies A-D, are summarized in the Declaration of Steven M. Watkins, submitted herewith. The results of Study A demonstrate the positive correlation of both (a) palmitoleic acid in cholesterol esters (CE16:1n7) and (b) the ratio of palmitoleic acid to palmitic acid in cholesterol esters (CE16:1n7/CE16:0) in blood to the expression of fatty acid synthase (FAS) in the liver. Study B showed that CE16:1n7 and the ratio of CE16:1n7 and CE16:0 were correlated with weight gain induced by treatment with a PPARgamma agonist. Study C provided data that CE16:1n7 and CE16:1n7/CE16:0 correlated with rosiglitazone treatment in humans. An additional study, Study D, provided data that serum levels of CE16:1n7 and CE16:1n7/CE16:0, markers which correlate with *de novo* fatty acid synthesis, were reduced during caloric restriction and weight loss.

Applicants contend that the specification *does* demonstrate that there is a correlation between (a) palmitoleic acid and the ratio of palmitoleic acid to palmitic acid in the cholesterol ester, phosphatidylcholine, and free fatty acid fractions from blood and (b) *de novo* fatty acid synthesis in the liver or adipose and weight gain/loss. Furthermore, these disclosures of the specification are further bolstered by the additional data provided in the Declaration of Steven M. Watkins submitted herewith. Accordingly, Applicants respectfully submit that the claims, as amended, are enabled for their full scope.

In light of the claim amendments, the remarks above, and the Declaration of Steven M. Watkins submitted herewith, Applicants respectfully request withdrawal of the rejection of claims 1, 8, 11-14, 21-22, 26-28, 30-35, 37, and 61-62 under 35 U.S.C. § 112, first paragraph.

Claim Rejections under 35 U.S.C. § 102

Rejection #1 under 35 U.S.C § 102:

Claims 1, 21, 61, and 62 are rejected under 35 U.S.C. § 102(b) as being anticipated by the Volpe et al. reference. In rejecting the claims, the Examiner states, "Volpe *et al.* disclose the administration of glucocortidcoid [*sic*] to glial cells and the measurement of the de novo synthesis of fatty acids in the glial cells, specifically palmitic acid by measuring the activity of fatty acid synthetase" (page 6 of Office Action mailed December 27, 2006). Applicants respectfully traverse this rejection.

As already noted above, claim 1, as amended, is directed to a method of assessing de novo fatty acid synthesis in a tissue of an organism, comprising quantifying a marker of de novo fatty acid synthesis in a biological sample from the organism, wherein the biological sample is a blood product, and wherein the marker of *de novo* fatty acid synthesis comprises: (a) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the free fatty acid fraction of the blood product, wherein the method is a method to assess *de novo* fatty acid synthesis in adipose tissue; or (b) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the phosphatidylcholine or cholesterol ester fraction of the blood product, wherein the method is a method to assess *de novo* fatty acid synthesis in liver tissue. Claims 21, 61, and 62 depend from claim 1 and therefore incorporate all elements of claim 1.

To anticipate a claim, a prior art reference must teach or suggest each and every limitation of the claim. Applicants respectfully contend that the Volpe et al. reference does not anticipate claims 1, 21, 61, and 62 because the reference does not teach or suggest each and every element of these claims. The Volpe et al. reference does not teach a method of assessing *de novo* fatty acid synthesis in a tissue of an organism, comprising quantifying a marker of *de novo* fatty

acid synthesis in a biological sample from the organism, wherein the biological sample is a blood product, and wherein the marker of *de novo* fatty acid synthesis comprises: (a) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the free fatty acid fraction of the blood product, wherein the method is a method to assess *de novo* fatty acid synthesis in adipose tissue; or (b) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the phosphatidylcholine or cholesterol ester fraction of the blood product, wherein the method is a method to assess *de novo* fatty acid synthesis in liver tissue. For example, the Volpe et al. reference relates to the study of C-6 glial cells in culture, and therefore neither discloses nor suggests the use of any markers, let alone palmitoleic acid (with or without palmitic acid), quantified from a blood product sample from an organism. As an additional example, the Volpe et al. reference does not report the use of markers that correlate with *de novo* fatty acid synthesis in particular tissues such as the liver.

Since the Volpe et al. reference does not teach or suggest each and every element of claims 1, 21, 61, and 62, Applicants respectfully request that the rejection of claims 1, 21, 61, and 62 under 35 U.S.C. § 102(b) be withdrawn.

Rejection #2 under 35 U.S.C § 102:

Claims 1, 2, 6-9, 11, 12, 14, 21-23, 30, 32, 37 and 62 are rejected under 35 U.S.C. § 102(a) as being anticipated by the Pruzanski et al. reference. In rejecting the claims, the Examiner states, "Pruzanski et al. measure fatty acid content and type in cholesterol esters from normal and acute-phase HDL (Table 2)" (page 6 of the Office Action mailed December 27, 2006). Applicants respectfully traverse this rejection.

Claims 2, 6, 7, 9, and 23 have been cancelled by this Amendment, and therefore, the rejection with respect to these claims is moot. Claim 1 is as described above with respect to the rejection over the Volpe et al. reference. Claims 8, 11, 12, 14, 21-22, 30, 32, 37 and 62 each depend, directly or indirectly, from claim 1 and therefore include all limitations of claim 1.

As noted above, to anticipate a claim, a prior art reference must teach or suggest each and every limitation of the claim. Applicants respectfully contend that the Pruzanski et al. reference does not anticipate claims 1, 8, 11, 12, 14, 21-22, 30, 32, 37 and 62 because the reference does not teach or suggest each and every element of these claims. The Pruzanski et al. reference does not teach a method of assessing *de novo* fatty acid synthesis in a tissue of an organism, comprising quantifying a marker of *de novo* fatty acid synthesis in a biological sample from the organism, wherein the biological sample is a blood product, and wherein the marker of *de novo* fatty acid synthesis comprises: (a) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the free fatty acid fraction of the blood product, wherein the method is a method to assess *de novo* fatty acid synthesis in adipose tissue; or (b) palmitoleic acid or both palmitoleic acid and palmitic acid quantified from the phosphatidylcholine or cholesterol ester fraction of the blood product, wherein the method is a method to assess *de novo* fatty acid synthesis in liver tissue. For instance, the Pruzanski et al. reference, while it may report differences in the lipid composition of normal HDL (NHDL) versus acute-phase HDL (APHDL), the reference does not report any correlation between fatty acids in the lipid compositions reported for NHDL and/or APHDL and *de novo* fatty acid synthesis in any tissues in the organism that would justify the use of the fatty acids as markers for *de novo* fatty acid synthesis in those tissues. Accordingly, the reference also fails to report any correlation between palmitoleic acid and/or palmitic acid with *de novo* fatty acid synthesis in specific tissues such as the liver.

Since the Pruzanski et al. reference does not teach or suggest each and every element of claims 1, 8, 11, 12, 14, 21-22, 30, 32, 37 and 62, Applicants respectfully request that the rejection of claims 1, 8, 11, 12, 14, 21-22, 30, 32, 37 and 62 under 35 U.S.C. § 102(a) be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 475512000400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 27, 2007

Respectfully submitted,

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